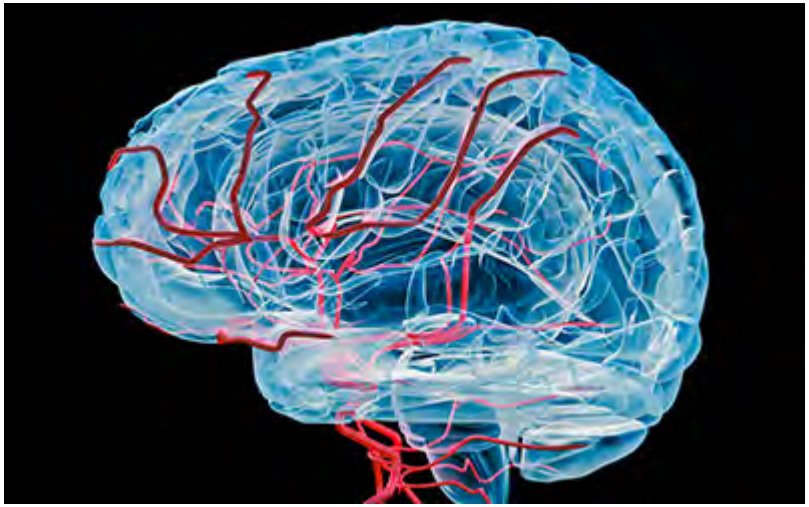
Vascular cognitive disorders

Dr Matt Paradise

Professor Perminder Sachdev



Centre for Healthy Brain Ageing (CHeBA)

Our Vision:

Our vision is to achieve, through research, healthier brain ageing and better clinical care of age-related brain diseases.

Scientia Professor Henry Brodaty

AO, MBBS, MD, DSc, FRACP, FRANZCP, FAHMS

- Consultant Old Age Psychiatrist & Head of the Memory Disorders Clinic, Prince of Wales Hospital, Sydney, Australia
- Scientia Professor of Ageing & Mental Health, University of New South Wales
- Centre Director, Dementia Centre for Research Collaboration — Assessment & Better Care (DCRC-ABC)

Scientia Professor Perminder Sachdev

AM, MD, PhD, FRANZCP, FAHMS

- Clinical Director, Neuropsychiatric Institute (NPI), Prince of Wales Hospital, Sydney, Australia
- Scientia Professor of Neuropsychiatry, University of New South Wales

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CHeBA Groups and Projects

Research Groups

- Epidemiology
- Genetics & Epigenomics
- Neuroimaging
- Neuropsychiatry
- Neuropsychology
- Omics and Neurobiology of Ageing

Longitudinal Studies

- Sydney Memory and Ageing Study
- Sydney Centenarian Study
- Older Australian Twins Study

CHeBA consists of 51 staff members and 26 students.

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Structure

Why cerebrovascular disease is important to cognition/dementia.

Why measuring it matters.

The problems with quantifying it.

What we do currently (and the problems with this)

Attempts to set common standards

Different approaches to quantification

My PhD

- How we are attempting to help with this problem

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Why CVD matters

CVD leading cause of morbidity and mortality

- large vessel disease → CVAs, multi-infarct dementia
- small vessel disease (SVD) → lacunar stroke (1/4 ischaemic strokes), vascular cognitive impairment or dementia, gait disturbance, urinary incontinence and neuropsychiatric symptoms

Terminology

Vascular cognitive disorder (VCD)

- Vascular cognitive impairment (VCI)
- Vascular dementia (VaD)
- Vascular contributions to cognitive impairment and dementia (VCID)

Traditional model

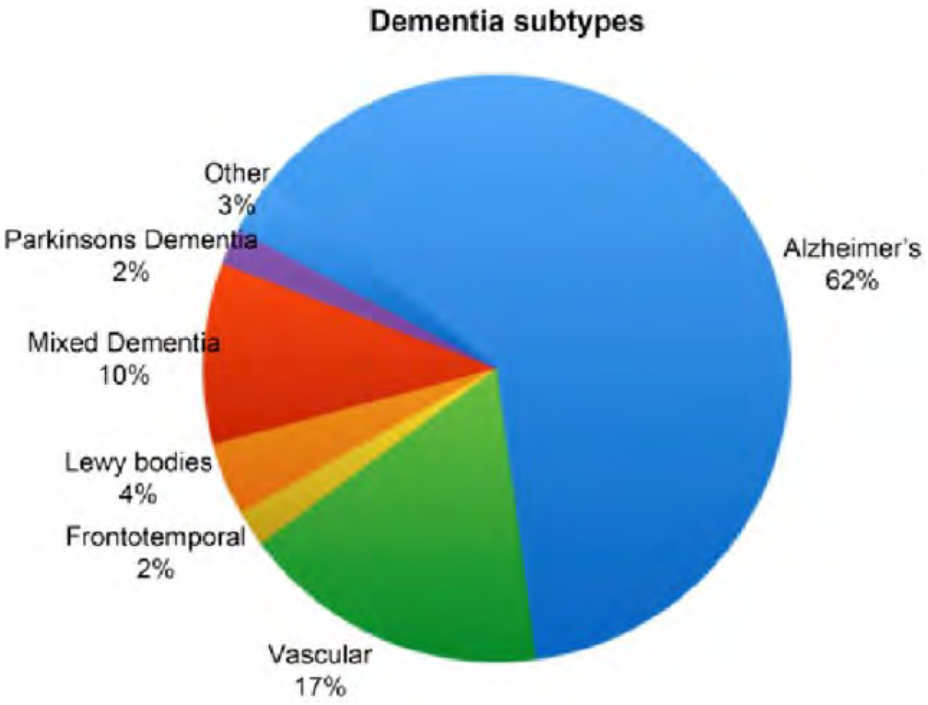

Fig. 1. The percentage occurrence of dementia subtypes

Alzheimer's Society. (2014). *Dementia UK: Update. Second edition.* London: Alzheimer's Society

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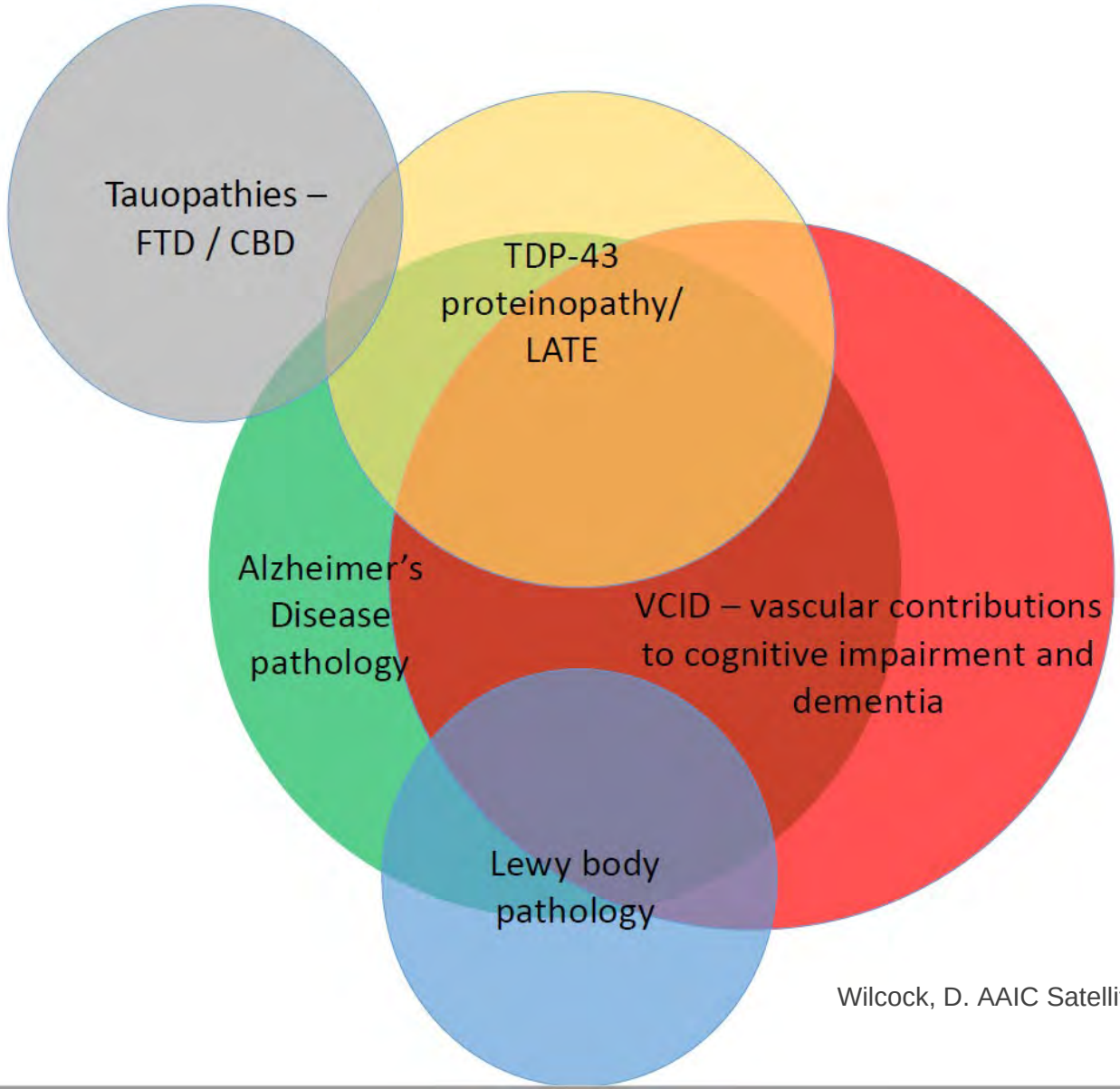
Real picture



Wilcock, D. AAIC Satellite Symposium, 2019

Real model

Table 3 Common lesions in AD, VaD, MIX, and aged controls (from [130])

Pathological feature	AD [%]	VaD [%]	MIX [%]	Aged controls [%]
Cerebral amyloid angiopathy	98	30	~90	23–45
Small vessel disease/MVD	~50	>50	>50	~20
Total infarctions	10–20	100	30–40	>10
Microinfarcts/lacunes	30–46	70	60–70	17–21
Intracerebral hemorrhage	10–15	15	10	1–2
White matter pathology	40	80	70–80	<20
Loss of cholinergic markers	75	40	~70	
CVD/atherosclerosis	45–60	60	~60	30–53

Abbreviations: AD, Alzheimer's disease; CVD, Cerebrovascular disease; MIX, mixed type dementia (AD plus vascular dementia); MVD, Microvascular disease; VaD, Vascular dementia.

Attems, J., & Jellinger, K. A. (2014). The overlap between vascular disease and Alzheimer's disease - lessons from pathology. *BMC Medicine, 12*(1), 206. doi:10.1186/s12916-014-0206-2

.

CVD worsens risk and expression of AD

- 50% to 84% of the brains of persons who die aged 80 to 90+ show appreciable cerebrovascular lesions
- AD and CVD share common risk factors such as hypertension during midlife, diabetes mellitus, smoking, apolipoprotein E (ApoE) ε4 isoforms, hypercholesterolemia, homocysteinemia, and, in particular, age
- Evidence that vascular risk factors have a deleterious effect on the expression and progression of dementia
- Insufficient evidence that altering vascular risk factor in dementia can slow progression

Diomedi, M., Misaggi, G. J. C., & Targets, N. D.-D. (2013). Vascular contribution to Alzheimer disease: predictors of rapid progression. *12*(4), 532-537.1.

Blom K, Emmelot-Vonk MH, Koek HL. The influence of vascular risk factors on cognitive decline in patients with dementia: A systematic review. Maturitas 2013;76:113-117

Valenti, R., Pantoni, L., & Markus, H. S. (2014). Treatment of vascular risk factors in patients with a diagnosis of Alzheimer's disease: a systematic review. *BMC Medicine, 12*(1), 160. doi:10.1186/s12916-014-0160-z)

Mechanisms

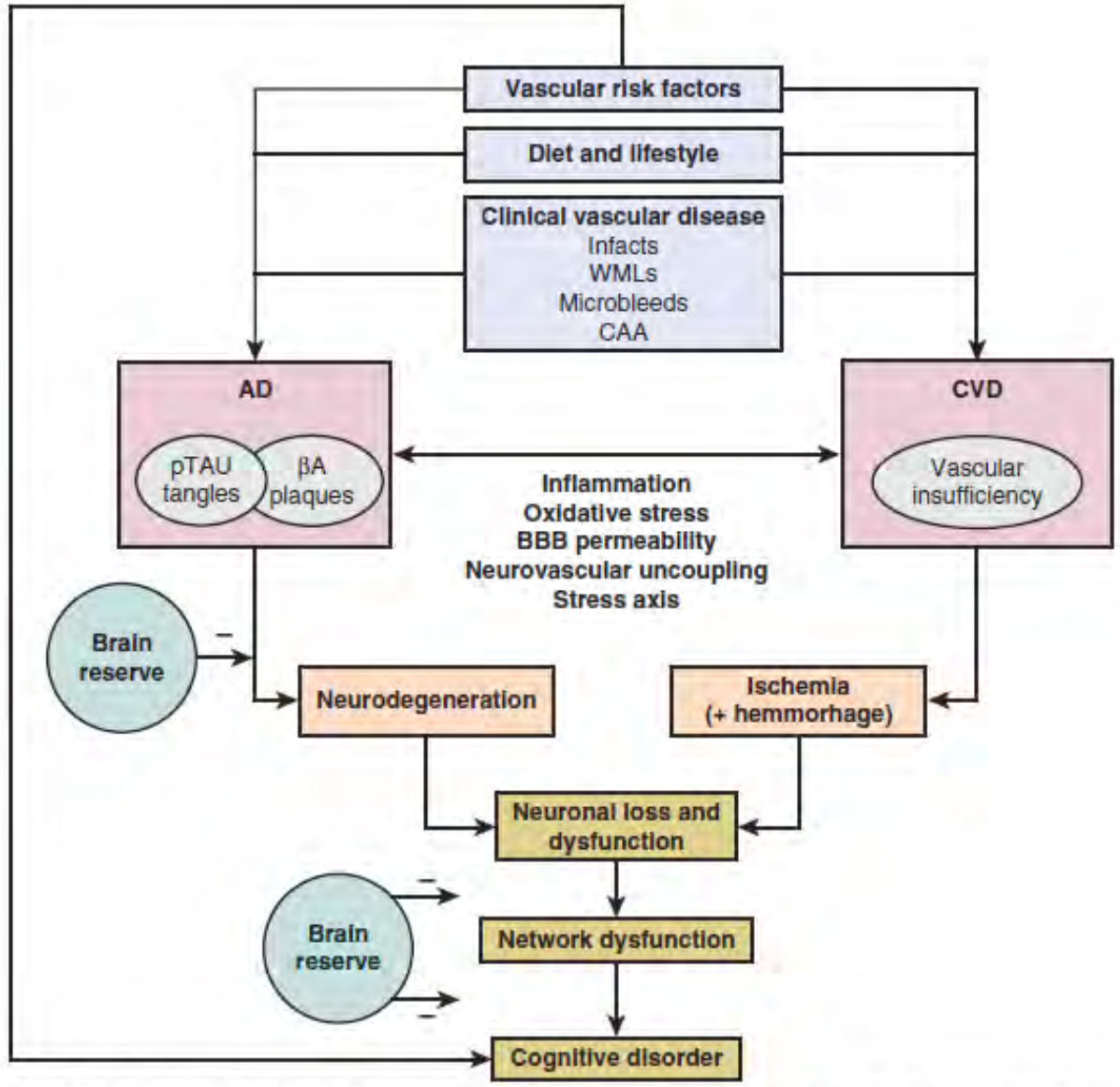
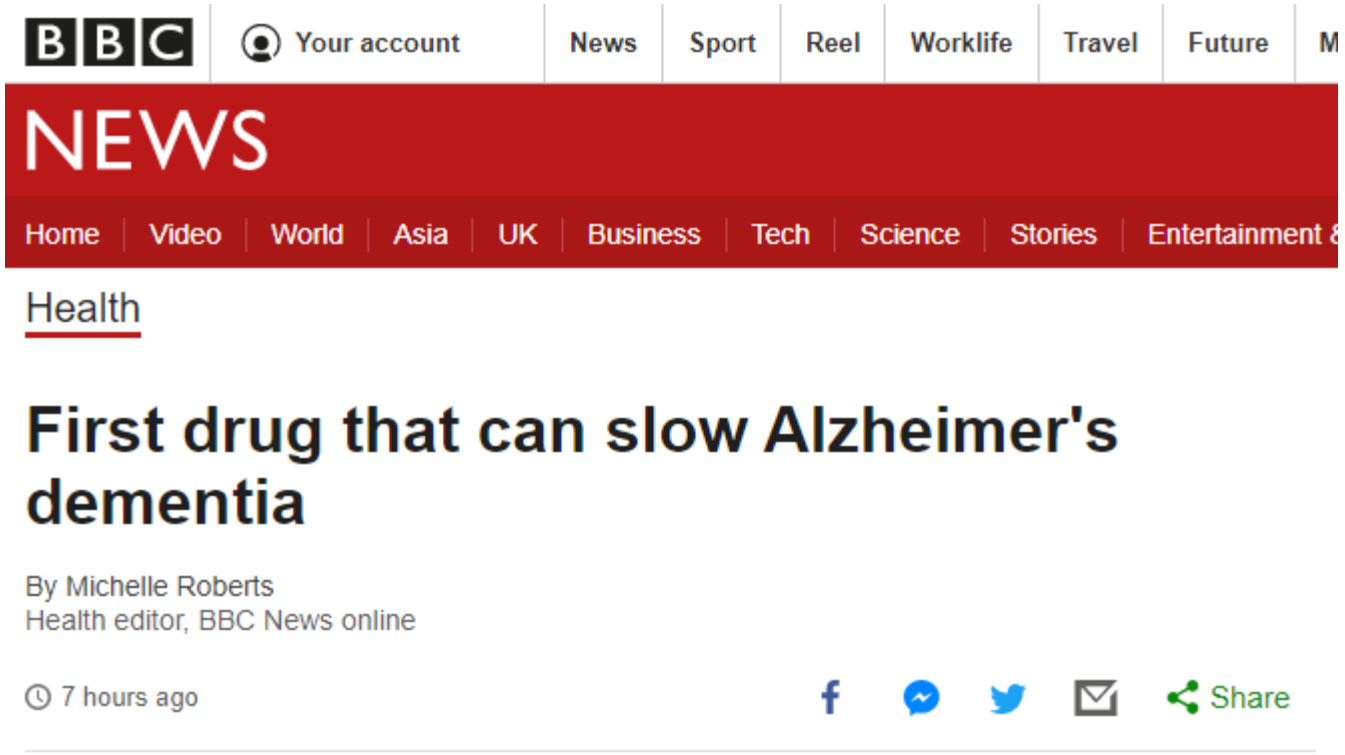


Figure 53-1. Proposed model for the vascular origins of dementia and interaction with Alzheimer's pathology. AD, Alzheimer disease; βA, β-amyloid protein; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; CVD, cerebrovascular disease; pTau, phosphorylated tau protein; WMLs, white matter lesions.

Sachdev P. Vascular cognitive disorders. In: Fillit HM, Rockwood K, Young J, B., eds. Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 8th edition ed. Philadelphia, PA: Elsevier, 2016.

Failure of AD disease modifying drugs…

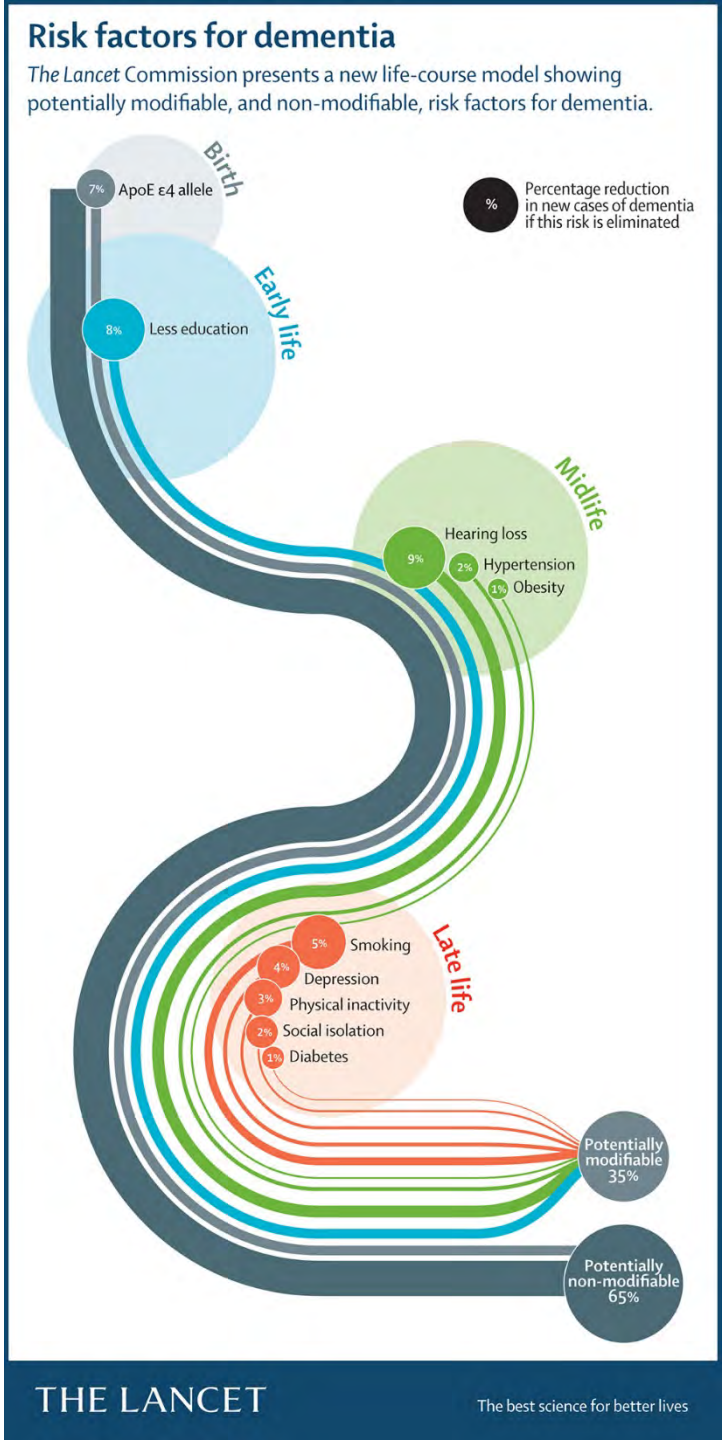
BREAKING NEWS !! - Aducanumab



Prevention of dementia

Modifiable risk factors:

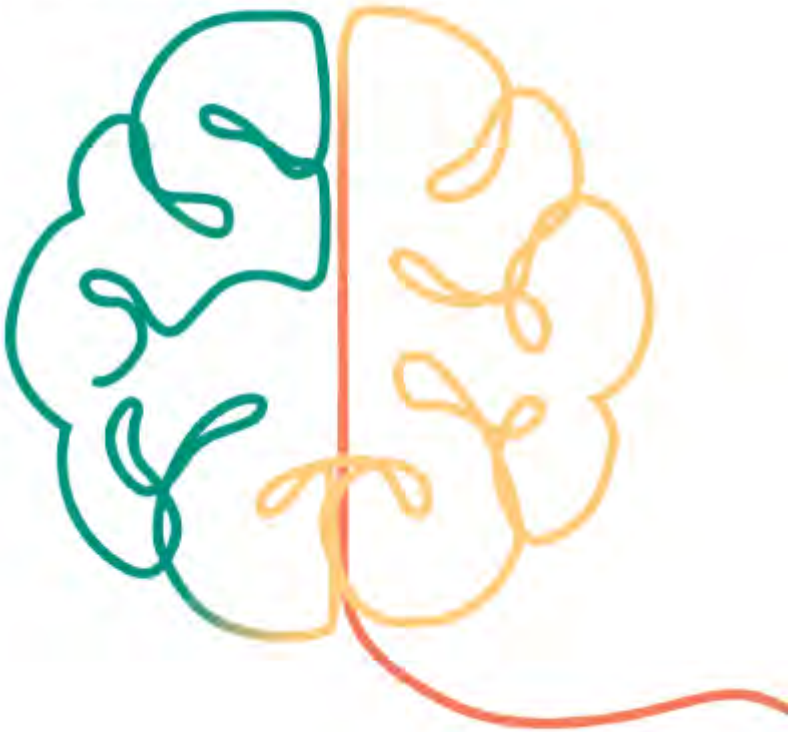
- Education
- Hearing loss
- Hypertension
- Obesity
- Smoking
- Depression
- Physical inactivity
- Social isolation
- Diabetes



Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734.

RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES



World Health Organization

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Physical activity interventions	**Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***
	Physical activity may be recommended to adults with mild cognitive impairment to reduce the risk of cognitive decline. *Quality of evidence:* ***low*** *Strength of the recommendation:* ***conditional***
Tobacco cessation interventions	**Interventions for tobacco cessation should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits.** *Quality of evidence:* ***low*** *Strength of the recommendation:* ***strong***
Nutritional interventions	**The Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***conditional***
	A healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet. *Quality of evidence:* ***low to high (for different dietary components)*** *Strength of the recommendation:* ***conditional***
	Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***
Interventions for alcohol use disorders	**Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits.** *Quality of evidence:* ***moderate (for observational evidence)*** *Strength of the recommendation:* ***conditional***
Cognitive interventions	**Cognitive training may be offered to older adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***very low to low*** *Strength of the recommendation:* ***conditional***
Social activity	**There is insufficient evidence for social activity and reduction of risk of cognitive decline/dementia.**
	Social participation and social support are strongly connected to good health and well-being throughout life and social inclusion should be supported over the life-course.

Weight management	**Interventions for mid-life overweight and/or obesity may be offered to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***low to moderate*** *Strength of the recommendation:* ***conditional***
Management of hypertension	**Management of hypertension should be offered to adults with hypertension according to existing WHO guidelines.** *Quality of evidence:* ***low to high (for different interventions)*** *Strength of the recommendation:* ***strong***
	Management of hypertension may be offered to adults with hypertension to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***very low (in relation to dementia outcomes)*** *Strength of the recommendation:* ***conditional***
Management of diabetes mellitus	**The management of diabetes in the form of medications and/or lifestyle interventions should be offered to adults with diabetes according to existing WHO guidelines.** *Quality of evidence:* ***very low to moderate (for different interventions)*** *Strength of the recommendation:* ***strong***
	The management of diabetes may be offered to adults with diabetes to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***very low*** *Strength of the recommendation:* ***conditional***
Management of dyslipidaemia	**Management of dyslipidaemia at mid-life may be offered to reduce the risk of cognitive decline and dementia.** *Quality of evidence:* ***low*** *Strength of the recommendation:* ***conditional***
Management of depression	**There is currently insufficient evidence to recommend the use of antidepressant medicines for reducing the risk of cognitive decline and/or dementia.**
	The management of depression in the form of antidepressants and/or psychological interventions should be provided to adults with depression according to existing WHO mhGAP guidelines.
Management of hearing loss	**There is insufficient evidence to recommend use of hearing aids to reduce the risk of cognitive decline and/or dementia.**
	Screening followed by provision of hearing aids should be offered to older people for timely identification and management of hearing loss as recommended in the WHO ICOPE guidelines.

Decreasing incidence of dementia?

Table 2. Temporal Trends in the Incidence of Dementia.*

Subtype	No. of Cases	Total No. of Observation Periods	5-Yr Cumulative Hazard Rate (95% CI)†				5-Yr Hazard Ratio (95% CI)‡				P Value for Trend
			Epoch 1	Epoch 2	Epoch 3	Epoch 4	Epoch 2	Epoch 3	Epoch 4	Trend§	
Overall dementia	371	9015	3.6 (2.9–4.4)	2.8 (2.2–3.5)	2.2 (1.8–2.8)	2.0 (1.5–2.6)	0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)	0.80 (0.72–0.90)	<0.001
Alzheimer's disease	264	9015	2.0 (1.5–2.6)	2.0 (1.5–2.6)	1.7 (1.3–2.3)	1.4 (1.0–1.9)	1.00 (0.70–1.43)	0.88 (0.62–1.25)	0.70 (0.48–1.03)	0.88 (0.77–1.00)	0.052
Vascular dementia	84	9014	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.89 (0.51–1.56)	0.46 (0.25–0.86)	0.45 (0.23–0.87)	0.71 (0.56–0.90)	0.004

* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.
† The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.
‡ The 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex.
§ We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.

Satizabal, C. L., Beiser, A. S., Chouraki, V., Chêne, G., Dufouil, C., & Seshadri, S. (2016). Incidence of Dementia over Three Decades in the Framingham Heart Study. *New England Journal of Medicine, 374*(6), 523-532. doi:10.1056/NEJMoa1504327

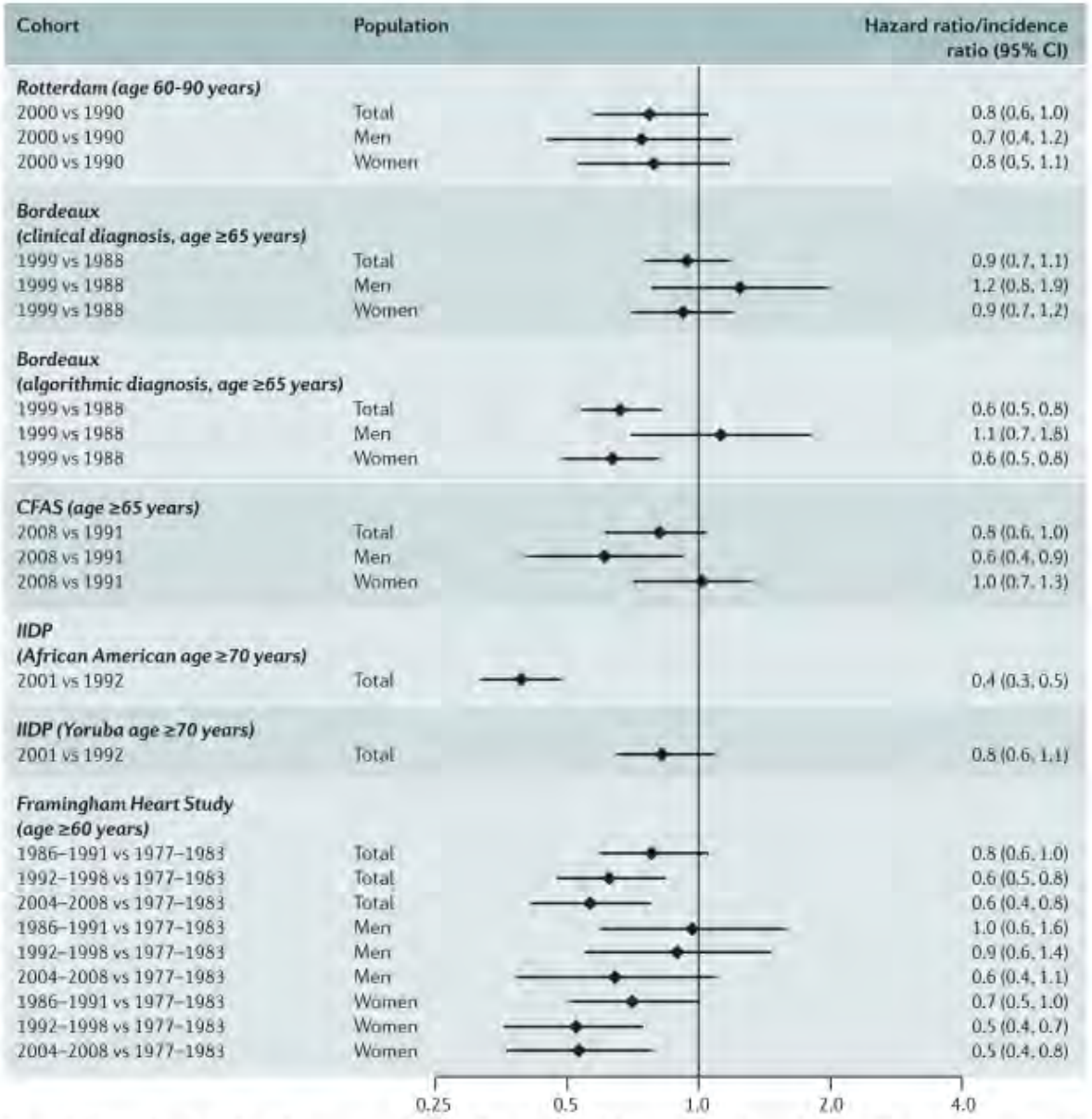

Figure 2 | **Hazard ratio and incidence rate ratio from five studies of dementia incidence.** Reported figures are the ratios of the incidence estimate in new cohorts to that in old cohorts. If incidence estimates remain the same across two cohorts, the ratio is 1.0. If estimates are higher in new cohorts than old cohorts, the ratio is greater than 1.0. Estimates are adjusted as follows: Rotterdam study, IIDP and Bordeaux study adjusted for age; Framingham Heart Study adjusted for age and sex; CFAS adjusted for age, sex, area and deprivation. In the Bordeaux study, clinical diagnosis was made by neuropsychologists and neurologists using criteria from the Diagnostic and Statistical Manual III revised and V, and algorithmic diagnosis was based on cognitive and functional ability tests. CFAS, Cognitive Function and Ageing Study; IIDP, Indianapolis–Ibadan Dementia Project.

Wu Y-T, Beiser AS, Breteler MMB et al. The changing prevalence and incidence of dementia over time - current evidence. Nature Reviews Neurology 2017; 13: 327-U379

Summary of importance

- CVD is common
- Leads to cognitive decline/dementia by itself and worsens risk and expression of AD.
- Potentially modifiable.

Why measuring CVD matters

Benefits

- Better diagnosis - distinguish between clinical phenotypes.
- Estimate risk and prognosis
- Monitoring of disease progression in an individual
- Neuroimaging as surrogate biomarker in prevention or treatment trials
  - Changes in CVD burden as proxy for longer term disease progression

Table 4. The predicted minimum sample size per arm (for MRI and cognitive measures) (power = 0.0.8 and type I error = 0.05) for a hypothetical clinical trial of 3-year duration assuming a balanced design with measurements taken every year evenly in time to test hypothetical treatment effects of 30, 25, 20, 15, and 10% in the intervention group.

	Sample size (per arm) to test treatment effects of:			
Parameter	30%	25%	20%	15%
MRI measures				
WMH volume	124	178	279	496
Brain Volume	145	208	325	578
Lacunes	572	842	1,345	2,442
MD normalized peak height	128	185	289	513
Cognitive indices				
Executive function	6,135	8,834	13,803	24,539
Processing speed	26,369	37,972	59,331	105,478

Abbreviations: MD, mean diffusivity; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

Benjamin P, Zeestraten E, Lambert C, et al. Progression of MRI markers in cerebral small vessel disease: Sample size considerations for clinical trials. J Cereb Blood Flow Metab 2016;36:228-240.

Challenges of CVD quantification

- Multiple lesion types
- Lesions relate to one another
- Variability in the outcome of any lesion – size, location
- Cannot directly visualise small vessels
- Poor correlation between WMH and cognition
- Visualisation of lesions dependent on technology –i.e., PVS, micro-infarcts
- Lesions may represent multiple pathologies (i.e., vascular and degenerative)
- Determining the necessary threshold for diagnosis – what is pathological?

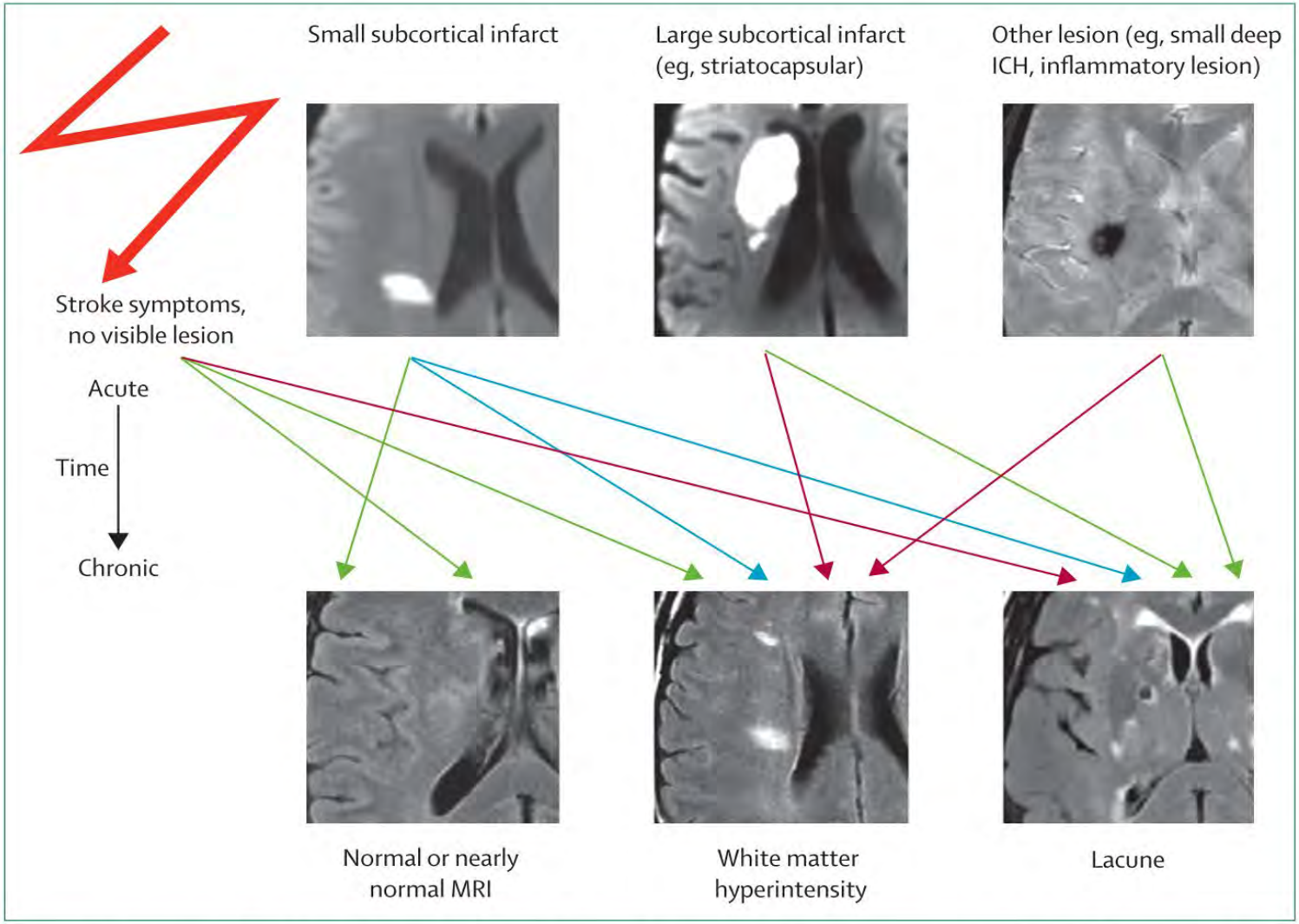

Figure 1: **Variable fates of lesions related to small vessel disease and the convergence of acute lesions with different causes but similar late appearances on MRI**

Arrows indicate possible late fates of acute MRI findings. Blue arrows indicate common fates of recent small subcortical infarcts, green arrows indicate less common fates, and red lines indicate least common late fates. ICH=intracranial haemorrhage.

Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822-838.

Different lesions and aetiologies

Large vessel disease	• Multiple infarcts • Single strategically placed infarct
Small vessel disease	• Multiple lacunar infarcts in white matter and deep gray matter nuclei • Ischemic white matter change • Dilation of perivascular spaces • Cortical microinfarcts • Cortical and subcortical microbleeds
Hemorrhage	• Intracerebral hemorrhage • Multiple cortical and subcortical microbleeds • Subarachnoid hemorrhage
Hypoperfusion	• Hippocampal sclerosis • Laminar cortical sclerosis

Panel: Aetiopathogenic classification of cerebral small vessel diseases

Type 1: arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)
Fibrinoid necrosis
Lipohyalinosis
Microatheroma
Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe)
Segmental arterial disorganisation

Type 2: sporadic and hereditary cerebral amyloid angiopathy

Type 3: inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy
For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations

Type 4: inflammatory and immunologically mediated small vessel diseases
For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis

Type 5: venous collagenosis

Type 6: other small vessel diseases
For example, post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

CADASIL=cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy.
CARASIL=cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy.
MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

Paradise MB, Sachdev PS. Vascular Cognitive Disorder. Semin Neurol 2019;39:241-250.

Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9:689-701.

Validation

- No gold standard
- Cognition – global, APS, executive, dementia diagnosis.
- Neuropathology.

Table 3 Neuropathology indices of cerebrovascular disease (CVD)

Study	Characteristics	Neuropathologic markers of CVD	Outcome measures
Esiri et al.[33]	18 NC, 19 CVD without dementia, 24 VaD	Semiquantitatively 0–3 ordinal scale of SVD based on widening of PVS, hyaline thickening of arteriolar walls, myelin pallor, nerve fiber attenuation/loss with gliosis	Dementia diagnosis
Gold et al.[57]	72 Patients without significant AD or macrovascular lesions	0–6 Vascular score based on cortical microinfarcts and basal ganglia and thalamic lacunes	Cognitive status (CDR)
Chui et al.[41]	79 Patients with subcortical ischemic vascular disease and AD	0–300 Cerebrovascular parenchymal pathology scores based on number and location of cystic, lacunar, and microinfarcts in gray and white regions and white matter demyelination	Cognitive status (CDR) and *APOE* genotype
Gold et al.[58]	156 Patients with AD pathology	0–30 Vascular score based on: cortical microinfarcts and basal ganglia and thalamic lacunes	Dementia diagnosis and subtype
Strozyk et al.[32]	190 Patients with diagnoses of dementia, AD, and VaD	Macroscopic vascular lesion score (0–6) based on large infarcts, lacunar infarcts (0, 1, and ≥2), and leukoencephalopathy (none, mild, moderate to severe)	Dementia diagnosis and subtype
Smallwood et al.[35]	70 Patients with CVD, excluding significant AD pathology	0–12 SVD pathology score based on pallor of myelin staining, myelin loss, loosening of parenchymal tissue extending in places to cavitation, and dilation of perivascular spaces	Cognition (MMSE and CAMDEX)
Deramecourt et al.[31]	135 Dementia cases of mixed pathology	0–20 Vascular score based on: vessel wall modification (arteriolosclerosis and amyloid angiopathy), perivascular hemosiderin leakage, perivascular space dilatation, myelin loss and cortical micro- or large infarcts	Neuropathologic diagnoses: VaD, AD, DLB
Jung et al.[59]	16 Subcortical ischemic vascular disease, 20 AD, 10 mixed pathology, and 17 NC	Chui et al.[41] index	Neuropathologic diagnosis: vascular disease, AD, mixed pathology, NC
Esiri et al.[34]	161 AD cases	Smallwood et al.[35] index	Cognitive scores (MMSE)
Skrobot et al.[11]	113 Patients without significant neurodegenerative disease	3 component model based on presence of moderate/severe occipital leptomeningeal CAA, moderate/severe arteriolosclerosis in occipital white matter, and ≥1 large infarct	Cognitive impairment (dementia or MCI)
Ezzati et al.[60]	62 Patients without dementia	Strozyk et al.[32]	Cognitive decline: Blessed information memory concentration score

Abbreviations: AD = Alzheimer dementia; CAA = cerebral amyloid angiopathy; CAMDEX = Cambridge Mental Disorders of the Elderly Examination; CDR = Clinical Dementia Rating scale; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = normal controls; PVS = perivascular spaces; SVD = small vessel disease; VaD = vascular dementia.

Paradise MB, Shepherd CE, Wen W, Sachdev PS. Neuroimaging and neuropathology indices of cerebrovascular disease burden: A systematic review. Neurology 2018;91:310-320.

doi:10.1093/brain/aww214 BRAIN 2016: 139; 2957–2969 | 2957

BRAIN
A JOURNAL OF NEUROLOGY

Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment

Olivia A. Skrobot,[1] Johannes Attems,[2] Margaret Esiri,[3] Tibor Hortobágyi,[4,5] James W. Ironside,[6] Rajesh N. Kalaria,[2] Andrew King,[7] George A. Lammie,[8] David Mann,[9] James Neal,[10] Yoav Ben-Shlomo,[11] Patrick G. Kehoe[1] and Seth Love[1]

Likelihood that cerebral vascular disease contributed to cognitive impairment		Low (<50%)			Moderate (50-80%)		High (>80%)		
One or more large (> 10 mm) subcortical cerebral infarcts		-	-	-	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA		-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis		-	-	+	-	+	-	+	+

Figure 1 VCING model estimating the likelihood that cerebrovascular disease contributed to cognitive impairment. Combinations of the three main determinants—at least one large (>10 mm diameter) infarct, moderate/severe occipital leptomeningeal CAA, and moderate/severe arteriolosclerosis in the occipital white matter—are used to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case. Scale bars in the *top*, *middle* and *bottom* photomicrographs represent 1 mm, 250 μm and 100 μm, respectively.

Shifting sands…

Non-imaging approaches

Mark VCID

ENDOTHELIAL SIGNALING KIT – PLASMA

- Composite biomarker of three plasma proteins: VEGF-D, PIGF, and bFGF.
- Rationale is that endothelial dysfunction early in cerebrovascular disease causes compensatory upregulation of endothelial & angiogenesis signalling
- Longitudinal preliminary data showed that baseline signal predicts accelerated white matter injury and cognitive decline measured by a composite memory score
- Cross-sectional data demonstrate association of endothelial signalling with higher cerebral free water and lower whole-brain FA, even after controlling for presence of amyloid on PET.

Wilcock, D. Fluid biomarkers of cerebrovascular disease, https://www.alz.washington.edu/NONMEMBER/SPR19/Clin/09_Wilcock.pdf

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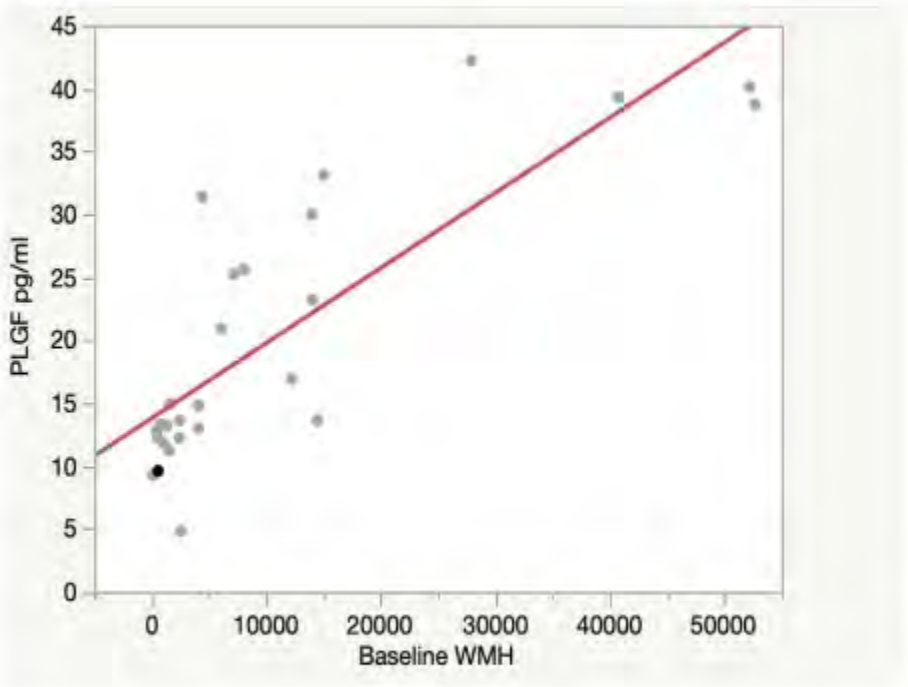
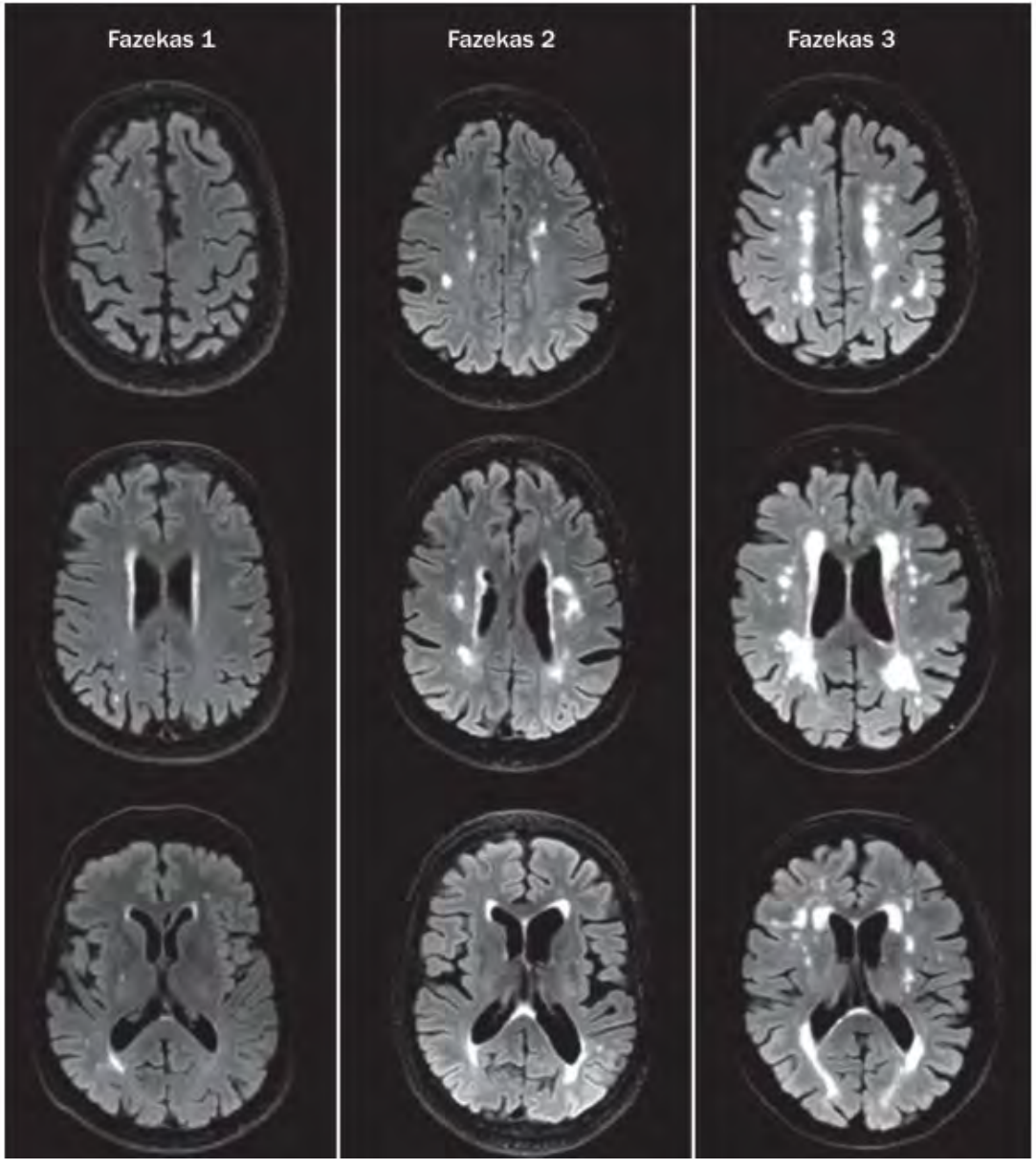
- CSF PLGF – placental growth factor, is significantly associated with WMH volume in a cohort of individuals who are cognitively normal or diagnosed with MCI and have high cardiovascular risk burden.
  - **P<0.001 for regression; R^2 = 0.679.**
- CSF PLGF measured using Quanterix Simoa.
- CSF PLGF also associates moderately with trail-making tasks and WAIS scores.
- CSF PLGF may be a promising biomarker for cerebral small vessel disease.



What we currently do…



Periventricular white matter (PVWM)

- 0 = absent
- 1 = “caps” or pencil-thin lining
- 2 = smooth “halo”
- 3 = irregular periventricular signal extending into the deep white matter

Deep white matter (DWM)

- 0 = absent
- 1 = punctate foci
- 2 = beginning confluence
- 3 = large confluent areas

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WMH

White matter hyperintensities (WMHs) are commonly seen on brain MRI in older people, and result from chronic ischaemia associated with cerebral small vessel disease

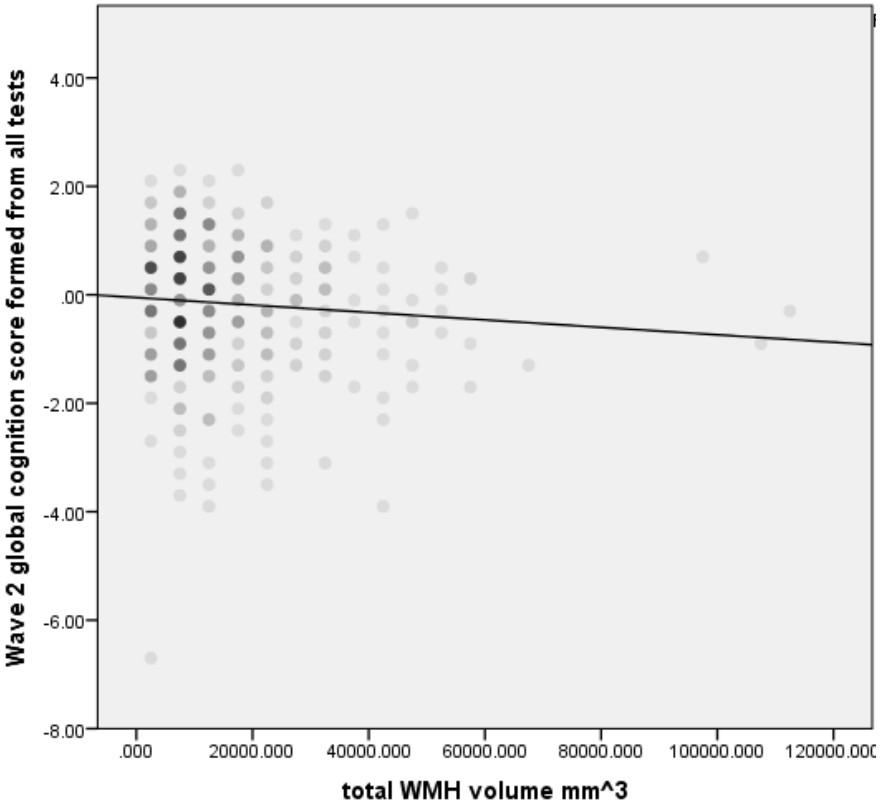
The histopathology of WMHs is heterogeneous, with tissue damage ranging from slight disentanglement of the matrix to varying degrees of myelin and axonal loss

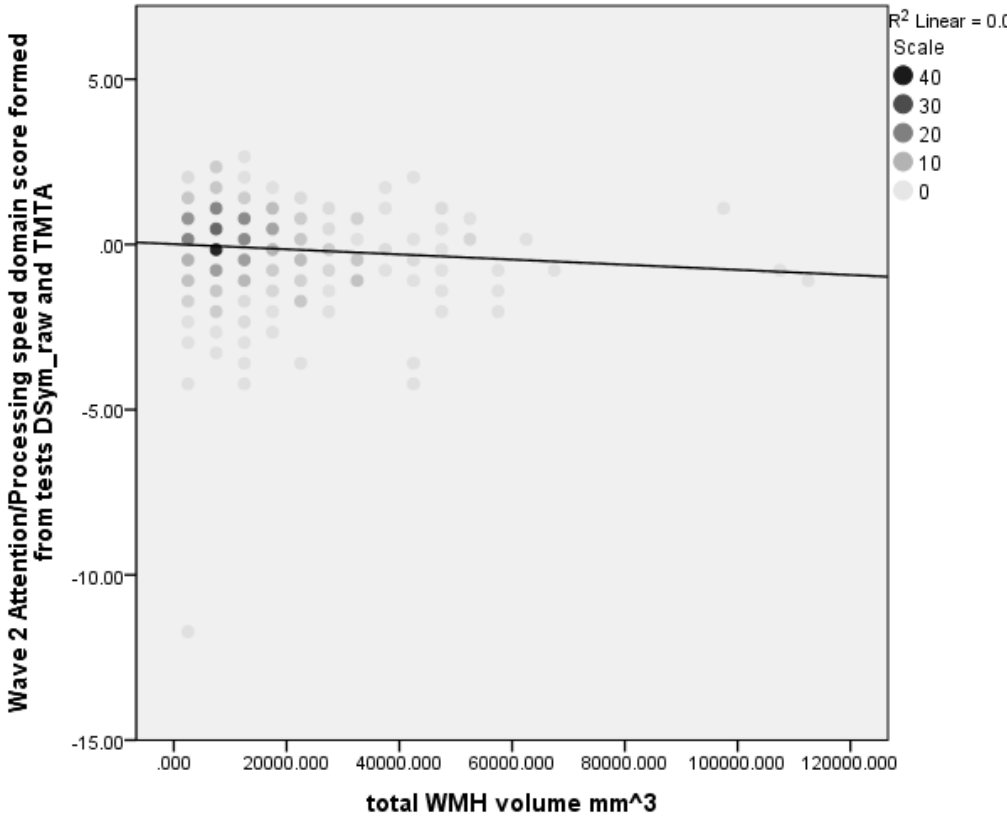
- axonal loss, enlargement of perivascular spaces, gliosis, myelin loss, and microglial activation.

This heterogeneity might partly explain the weak clinicoradiological associations found in patients with WMHs

Confluent WMH associated with dementia

WMH and cognition





Sydney memory and ageing study (unpublished)

Linear regression (unadjusted)

Beta -0.84, t=-1.9, p=0.09

Beta -0.91, t=-1.81, p=0.07

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Diagnostic criteria (neuroimaging requirements)

Diagnostic criteria	Construct	Neuroimaging criteria
DSM-IV [11]	Vascular dementia	Not specified
DSM-V	Vascular cognitive disorder	*Major*: multiple large, at least one which should be outside the cerebellum *Major or mild*: >2 lacunes outside the brainstem or single lacune in the striatum or the thalamus with a temporal relationship infarction and the cognitive syndrome, or extensive and confluent white matter lucencies
ADDTC [6]	Ischemic vascular dementia	Evidence of ≥2 strokes with at least one infarct outside the cerebellum by CT or T_1-weighted MRI, *or* Evidence of a single stroke with a clear temporal relationship between the stroke and cognitive presentation
ICD-10 [12]	Vascular dementia	Not specified
NINDS-AIREN [7]	Vascular dementia	Radiographic evidence of cerebrovascular disease (either multiple large vessel strokes or a single strategically placed infarct) *and a* temporal relationship between neuroimaging and clinical presentation **- or extensive periventricular WM lesions**

Vascular cognitive impairment. In: Godefroy O, ed. The Behavioral and Cognitive Neurology of Stroke, 2 ed. Cambridge: Cambridge University Press, 2013: 1-31.

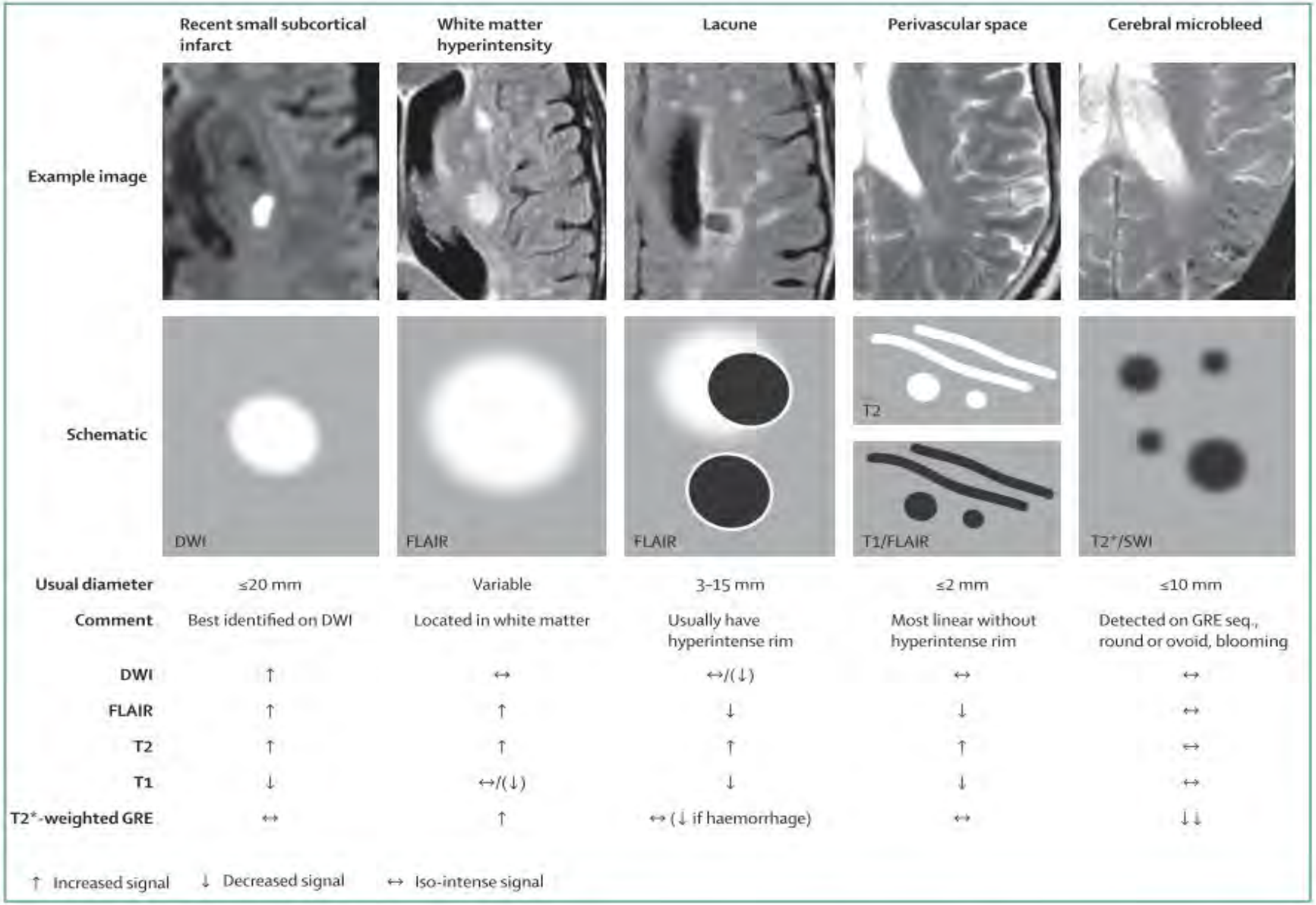
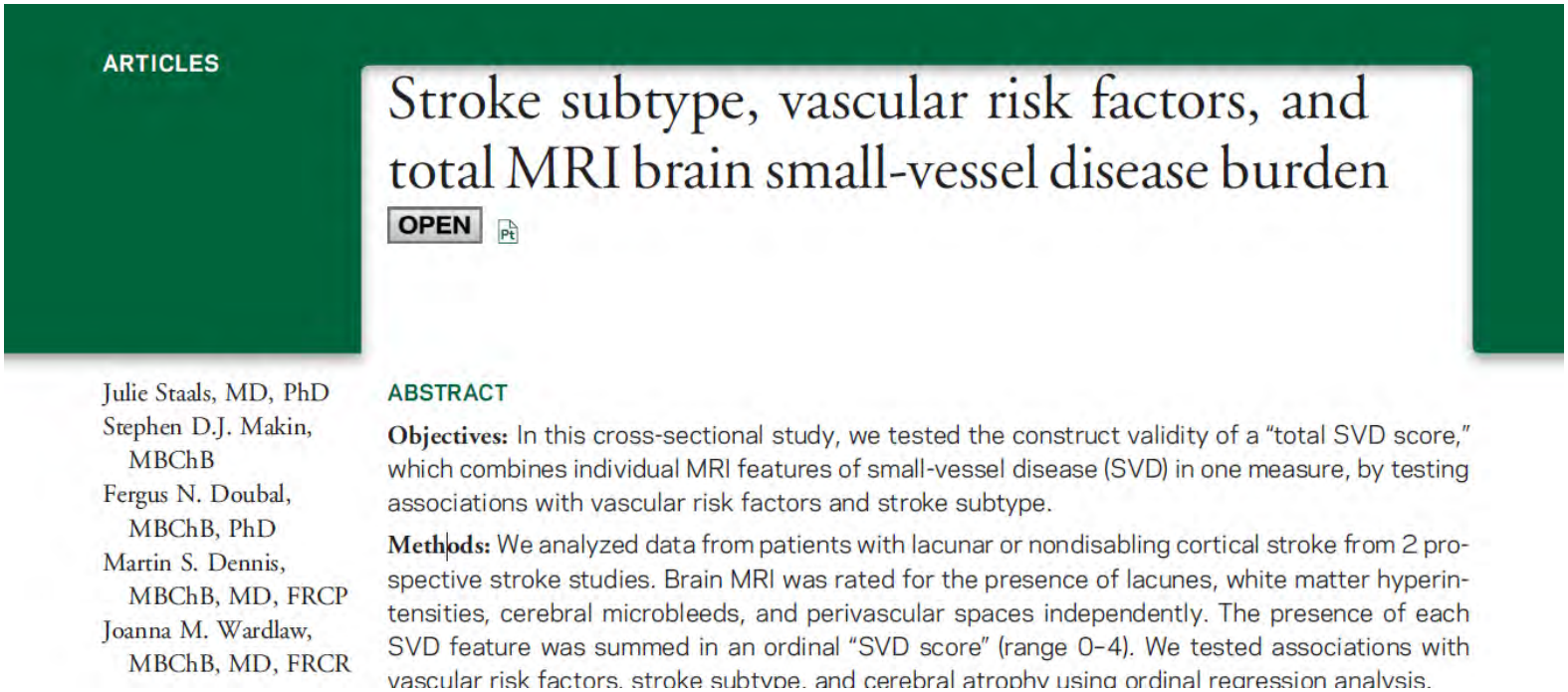


***Figure 2*: MRI findings for lesions related to small vessel disease**
Shows examples (upper) and schematic representation (middle) of MRI features for changes related to small vessel disease, with a summary of imaging characteristics (lower) for individual lesions. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery. SWI=susceptibility-weighted imaging. GRE=gradient-recalled echo.

Use of a composite CVD burden index



ARTICLES

Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden

OPEN

Julie Staals, MD, PhD
Stephen D.J. Makin, MBChB
Fergus N. Doubal, MBChB, PhD
Martin S. Dennis, MBChB, MD, FRCP
Joanna M. Wardlaw, MBChB, MD, FRCR

ABSTRACT

Objectives: In this cross-sectional study, we tested the construct validity of a "total SVD score," which combines individual MRI features of small-vessel disease (SVD) in one measure, by testing associations with vascular risk factors and stroke subtype.

Methods: We analyzed data from patients with lacunar or nondisabling cortical stroke from 2 prospective stroke studies. Brain MRI was rated for the presence of lacunes, white matter hyperintensities, cerebral microbleeds, and perivascular spaces independently. The presence of each SVD feature was summed in an ordinal "SVD score" (range 0–4). We tested associations with vascular risk factors, stroke subtype, and cerebral atrophy using ordinal regression analysis.

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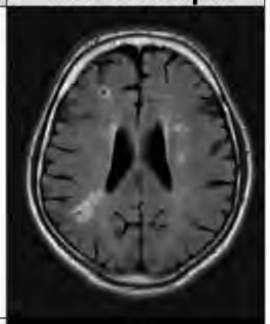
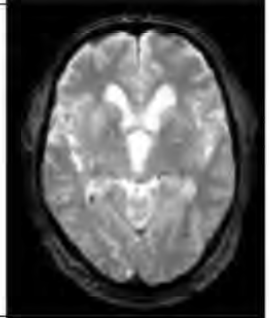
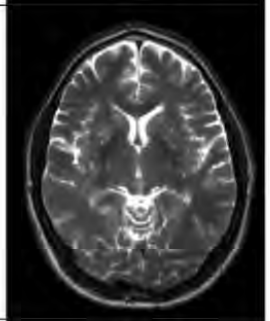
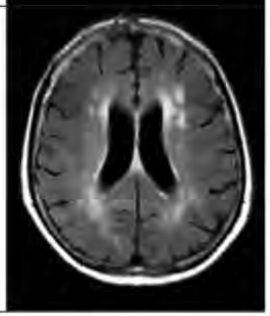
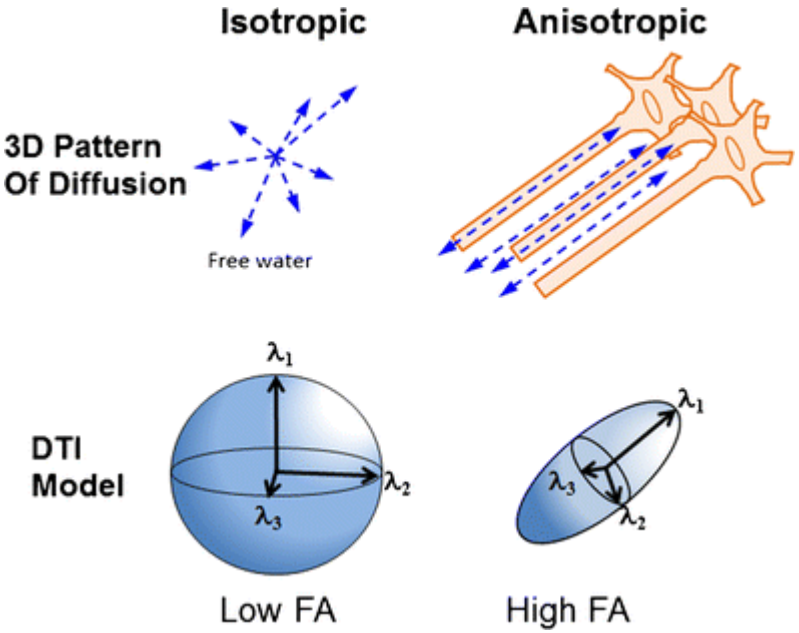
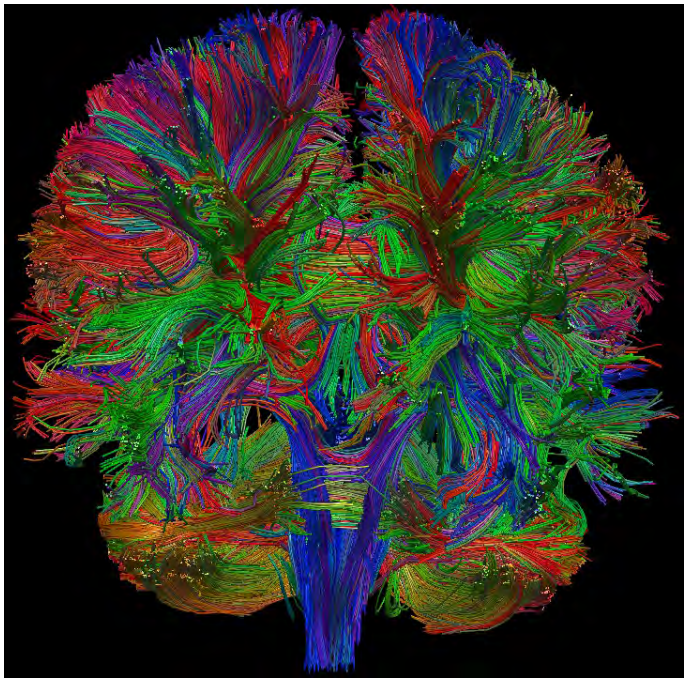
Figure Total small-vessel disease score features and categories

MRI feature	Visual assessment	Definition	Score	MRI example
Lacunes	International consensus definition[14]	≥1 Lacune	1 point	
Microbleeds	International consensus definition[14]	≥1 Microbleed	1 point	
Perivascular spaces	Semiquantitative scale[7]	Moderate to severe perivascular spaces in basal ganglia	1 point	
White matter hyperintensities (WMH)	Fazekas scale[19]	Periventricular WMH Fazekas 3 (extending into the deep white matter) and/or deep WMH Fazekas 2-3 (confluent or early confluent)	1 point	

Staals J, Makin SDJ, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology 2014;83:1228-1234.

Diffusion tensor imaging





A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms

Ebru Baykara, MSc,[1] Benno Gesierich, PhD,[1] Ruth Adam, PhD,[1]

ANN NEUROL 2016;80:581–592

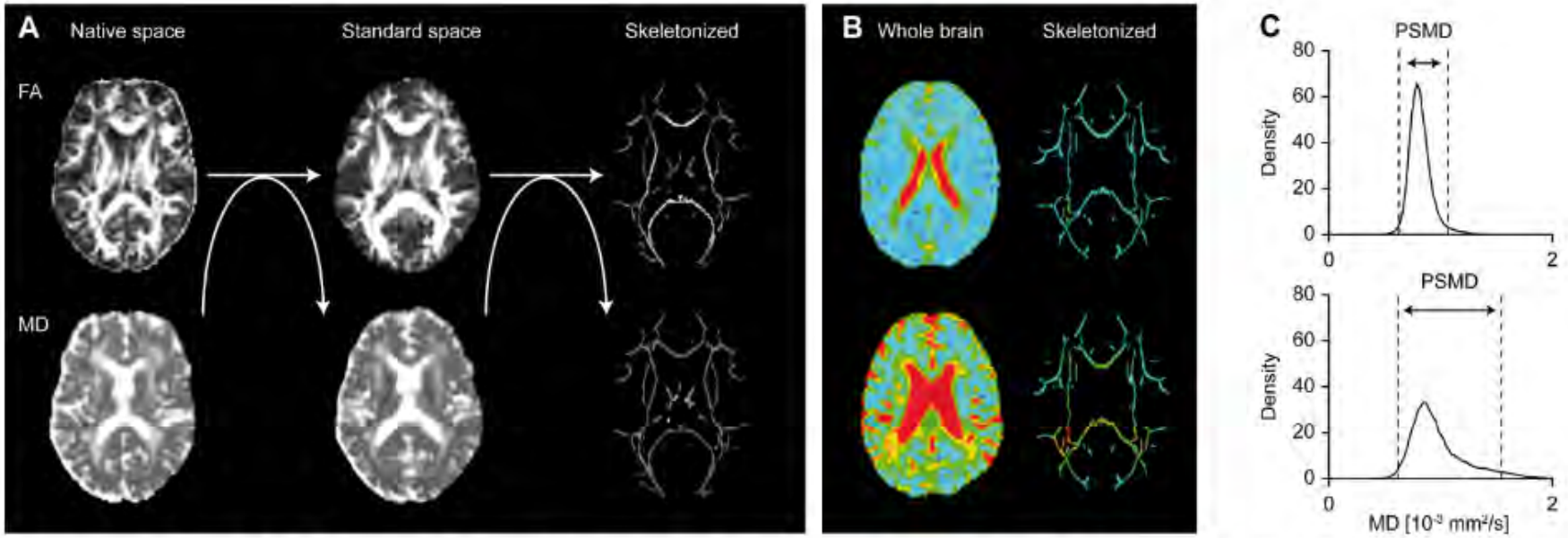


FIGURE 2: Procedure for marker calculation: skeletonization and histogram analysis. (A) Illustration of the automated skeletonization procedure. Individual fractional anisotropy (FA) images are normalized to standard space and projected onto the skeleton template. Next, the transformation and skeleton projection parameters are applied to the mean diffusivity (MD) images. (B) Examples of MD maps from 2 CADASIL subjects (upper and lower panel) projected onto the standard skeleton. (C) Histogram analysis of the same MD data as in B. Peak width of skeletonized MD (PSMD) is calculated as the difference between the 95th and 5th percentiles.

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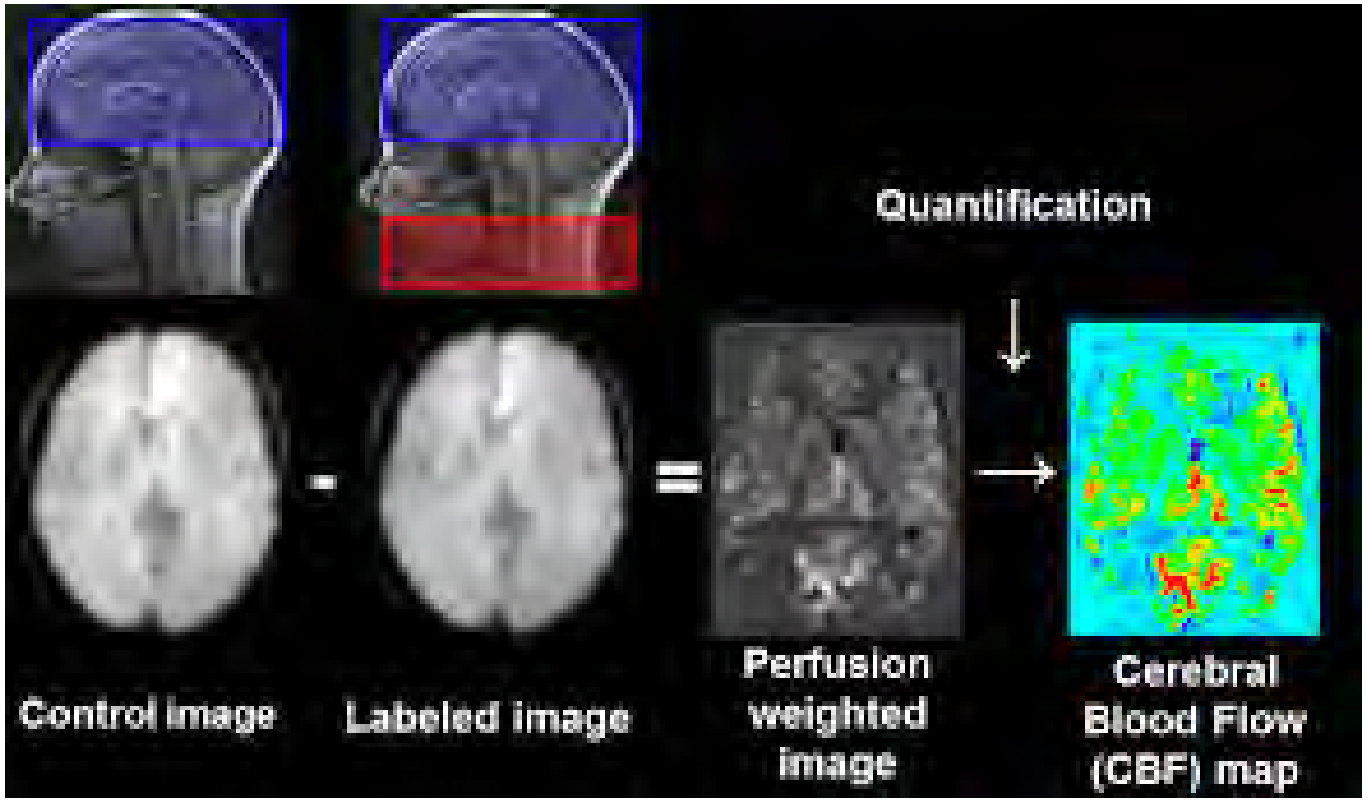
Perfusion – Arterial Spin Labelling



Construction of a novel CVD index

VIEWS & REVIEWS

Neuroimaging and neuropathology indices of cerebrovascular disease burden

A systematic review

Matthew B. Paradise, MBChB, MSc, Claire E. Shepherd, PhD, Wei Wen, PhD, and Perminder S. Sachdev, MD, PhD

Neurology® 2018;0:1-11. doi:10.1212/WNL.0000000000005997

Correspondence
Dr. Paradise
z3495052@ad.unsw.edu.au

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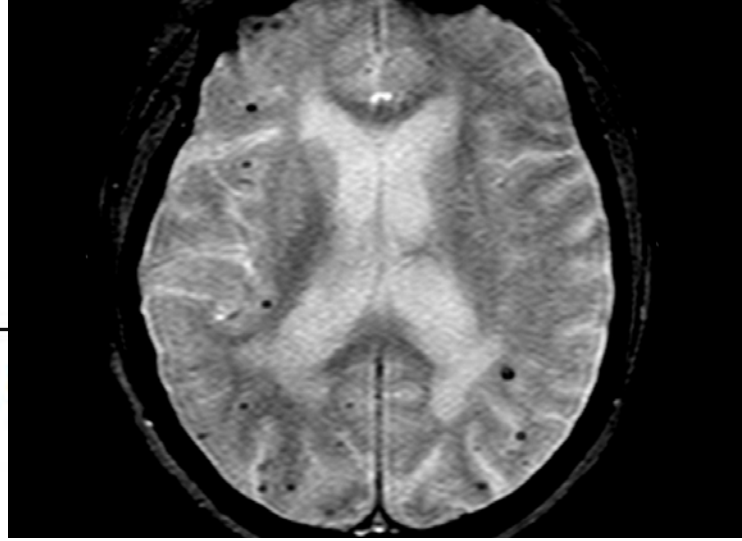
Cerebral microbleed (CMB)



Brain Imaging and Behavior
https://doi.org/10.1007/s11682-018-9883-3

ORIGINAL RESEARCH

The relationship of cerebral microbleeds to cognition and incident dementia in non-demented older individuals

Matt Paradise[1] · Adam Seruga[2] · John D. Crawford[1] · Joga Chaganti[3] · Anbupalam Thalamuthu[1] · Nicole A. Kochan[1,4] · Henry Brodaty[1,5] · Wei Wen[1,4] · Perminder S. Sachdev[1,4]

- 302 adults age 70-90 from Sydney Memory and Ageing Study
- Non-demented at baseline
- Relationship of CMB with neuropsychological defined cognitive testing and incident dementia examined cross-sectionally and longitudinally over 4 years.
- CMB visually rated on susceptibility weighted imaging. Trained in liaison with Neuroradiologist.

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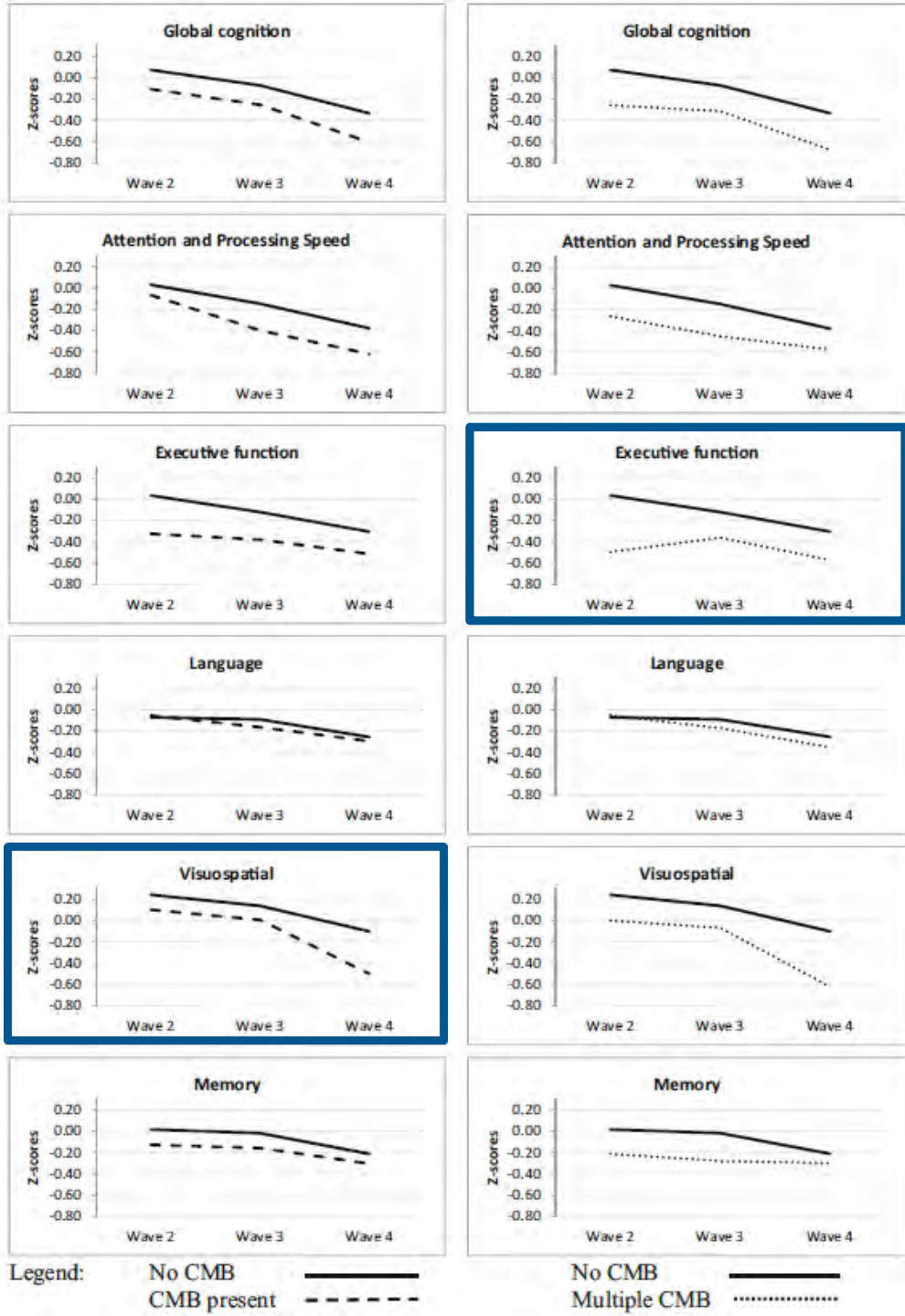
CMB

- Linear mixed modelling for continuous cognitive dependent variables.
- Logistic regression for incident dementia.

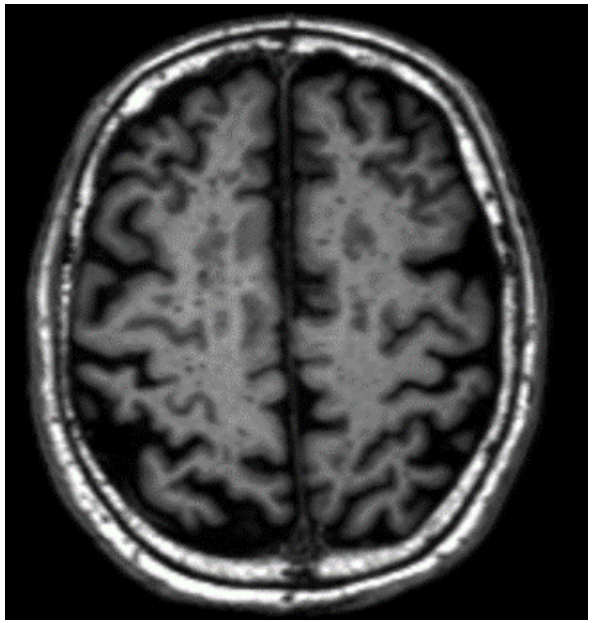
- Cross-sectional analysis – association with executive function.
- Longitudinal - association with decline in executive and VS function.
- No difference in incident dementia rates

Fig. 1 Estimated mean z-scores for global and specific cognitive domains, across waves 2, 3 and 4 (whole brain). Means adjusted for age, sex and education



Dilated perivascular spaces (PVS)

- Marker of SVD, commonly found in the basal ganglia and centrum semiovale.
- Frequent MRI finding in the elderly.
- The association with cognitive impairment, particularly longitudinal decline and incident dementia is unclear.



- PVS have to be visually rated
- Poor inter-rater reliability with existing scales – most scales use T2w as primary sequence. T1w has poorer contrast.

- We developed and validated of our own rating scale

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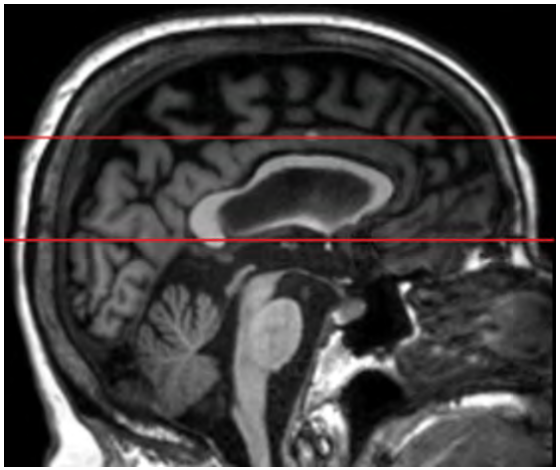
New visual rating scale of PVS

- 414 community dwelling older adults age 70-90 from MAS
- Two predetermined slices
- Construct validity: associations with age, sex, vascular risk factors and neuroimaging markers of SVD; WMH, lacunes and cerebral microbleeds. Basal ganglia PVS were associated with other SVD markers.
- Associations with cross sectional global and domain specific cognition were examined.
- Excellent psychometric properties: excellent inter-rater reliability (ICC - basal ganglia 0.82 and centrum semiovale 0.96), good intra-rater reliability (ICC in basal ganglia 0.72 and centrum semiovale 0.87).
- PVS in either location were not associated with global or domain specific cognitive impairment.



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The association of dilated PVS with cognitive decline and incident dementia (unpublished data)

	Severe basal ganglia PVS (dichotomized around top quartile)		Severe centrum semiovale PVS (dichotomized around top quartile)	
	Model 1 B (SE), p-value	Model 2 B (SE), p-value	Model 1 B (SE), p-value	Model 2 B (SE), p-value
Global Cognition	-0.07 (0.06), 0.22	-	**-0.16 (0.06), 0.01**	-0.13 (0.07), 0.08
Attention and Processing Speed (sqrt)	**-0.04 (0.01), 0.01**	-0.03 (0.02), 0.06	-0.02 (0.02), 0.30	-
Executive function (sqrt)	-0.03 (0.02), 0.11	-	-0.02 (0.02), 0.25	-
Language	-0.03 (0.06), 0.54	-	-0.06 (0.06), 0.37	-
Visuospatial function	-0.02 (0.05), 0.73	-	**-0.12 (0.06), 0.03**	-0.11 (0.06), 0.09
Memory	0.02 (0.05), 0.69	-	-0.09 (0.06), 0.09	-0.08 (0.06), 0.20
	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value
Dementia diagnosis	1.29 (0.78 - 2.12), 0.32	1.11 (0.66 – 1.88), 0.69	**2.73 (1.59 – 4.68), <0.001**	**2.61 (1.51 – 4.49), 0.001**

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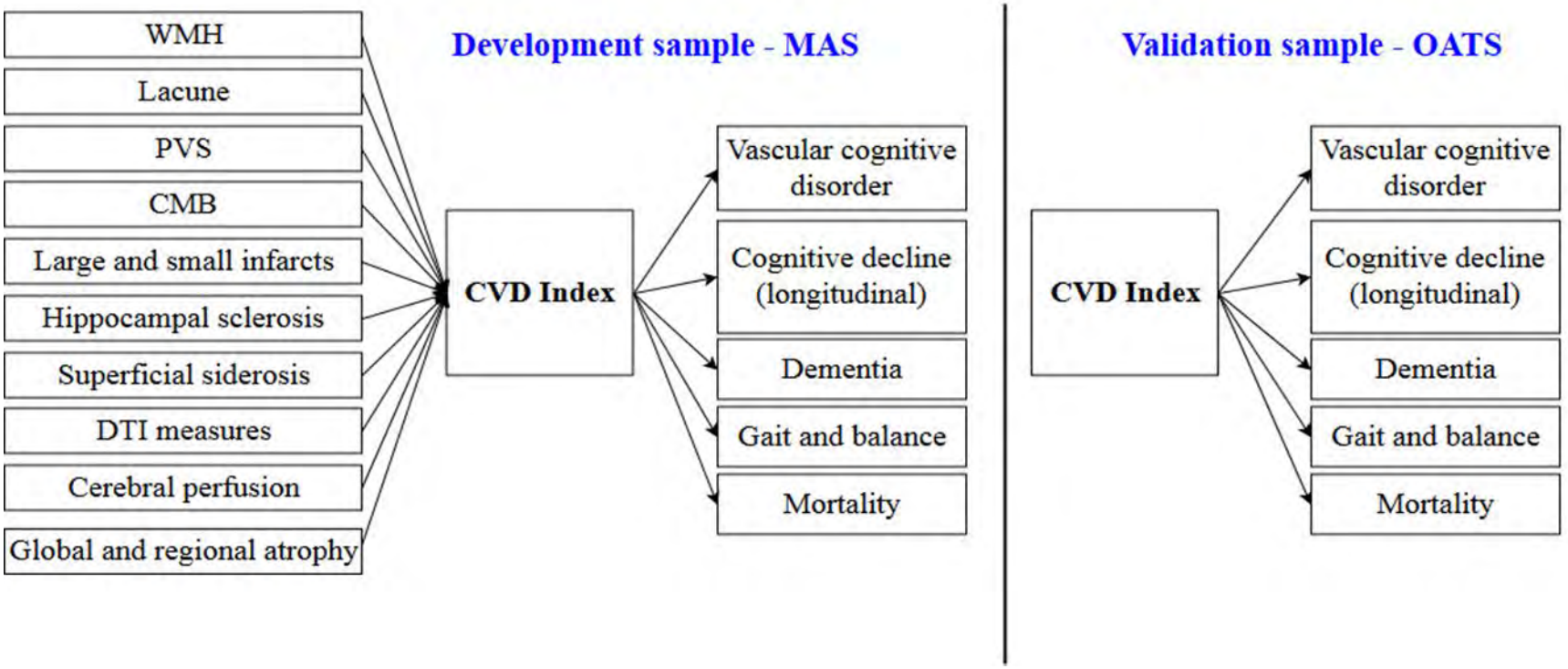
Future plans



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